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(71) Applicants *(for all designated States except US)*: AXCAN PHARMA INC. [CA/CA]; 597, boulevard Laurier, Mont Saint-Hilaire, Québec J3H 4XB (CA). ISTITUTO PIRRI S.R.L. [IT/IT]; Via Puccini, 3, I-20121 Milano (IT).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: SANSO', Giovanni [IT/IT]; Via Ponte Seveso, 23, I-20125 Milano (IT).

(74) Agent: RICCARDI, Sergio; Riccardi & Co., Via M. Melloni, 32, I-20129 Milano (IT).

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(54) Title: A DOUBLE CAPSULE FOR THE ADMINISTRATION OF ACTIVE PRINCIPLES IN MULTIPLE THERAPIES

(57) Abstract

A pharmaceutical dosage form particularly suitable for the administration of active principles in multiple therapies is disclosed. The pharmaceutical dosage form is a double capsule wherein an internal capsule is placed inside an external one. Each internal and external capsule includes one or more active principles. A double capsule according to the invention is preferably used in triple or quadruple therapies against the microorganisms Helicobacter Pylori. Advantages of this pharmaceutical dosage form consist in provididng a simple posology for administration of two and more active principles, allowing the active principles to activate at the right intervals of time and in the pre-established quantities, and preventing interactions between active principles. In a preferred embodiment of the invention, the pharmaceutical dosage form has an external capsule containing bismuth subcitrate and metronidazole, and an internal capsule containing tetracycline and optionally omeprazole, which is used in therapy for eradication of Helicobacter pylori.

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A DOUBLE CAPSULE FOR THE ADMINISTRATION OF ACTIVE PRINCIPLES IN MULTIPLE THERAPIES

FIELD OF THE INVENTION

This invention concerns a pharmaceutical dosage form consisting of a double capsule for the administration of active principles in multiple therapies. The double capsule consists in a capsule placed inside another one.

BACKGROUND OF THE INVENTION

Therapies for the administration of more than one active principle at a time or at short intervals of time are already well known. The most common pharmaceutical dosage form consists of tablets for the various active principles with coatings allowing the differentiated release of the chemical compounds.

Among said therapies, the most common ones are those concerning affections of the digestive system caused by the presence of the microorganisms Helicobacter Pylori, such as gastritis and gastroduodenal ulcers, which in due time can lead to tumoral forms. As known, Helicobacter pylori is a modern appellation of Campilobacter pylori.

Patent US-5 196 205 describes a method for the treatment of those pathological agents, consisting of the administration of a compound of bismuth, an antibiotic belonging to the group of penicillins and tetracycline and a second antibiotic such as metronidazole. The relevant therapy consists of the administration of three tablets (one for each active principle) several times a day.

Consequently, this therapy results in being extremely complicated.

The therapy described by patent US-5 196 205 has been further modified by the addition of a fourth active principle, omeprazole which reduces the gastric secretion by inhibiting irreversibly enzyme H+/K+ ATP. Omeprazole must be administered at a different time from the above-mentioned active principles, which are determined by the physician according to the seriousness of the disease, the age of the patient and other factors which could affect its efficacy.

Therefore, it can certainly be stated that therapies requiring a complicated posology such as multiple therapies, are subject to mistakes that can compromise the outcome of the therapy itself.

Other patents and patent applications describing single or multiple therapies for eradication of Helicobacter pylori are known such as US-5 472 695, US-5 560 912, US-5 582 837, WO 92/11848 and WO 96/02237. None of these previous patents and patent applications overcome the problem of the interaction between active principles by using a way as simple and ingenious than the one proposed by the present invention.

US-5 310 555 and US-5 501 857 teach to use double capsules for the delivery of nutritional supplements to animals but never suggest to use it for the administration of drugs in multiple therapies.

Among multiple therapies for eradication of Helicobacter pylori, the following combinations of active principles have been tested on humans, and published:

1. Amoxicilline, metronidazole and furazolidone;
2. Bi Subsalicylate, lansoprazole and clarithromycine;
3. Bi Subsalicylate, roxithromycine, metronidazole and ranitidine;
4. Clarithromycine, colloidal bismuth subcitrate and furazoline;
5. Colloidal bismuth subcitrate, amoxicilline and metronidazole;
6. Ebrotidine, amoxicilline and metronidazole;
7. Lansoprazole, amoxicilline and azithromycine;
8. Lansoprazole, amoxicilline and clarithromycine;
9. Lansoprazole, amoxicilline and rebamipide;
10. Lansoprazole, clarithromycine and furazoline;
11. Lansoprazole, azithromycine and metronidazole;
12. Lansoprazole, miconazole and amoxicilline;
13. Lansoprazole and norfloxacine;
14. Metronidazole and dirithromycine;

15. Omeprazole, amoxicilline and azithromycine;
16. Omeprazole, amoxicilline, clarithromycine and metronidazole;
17. Omeprazole, amoxicilline, metronidazole and bismuth;
18. Omeprazole, amoxicilline and rebamipide;
19. Omeprazole, amoxicilline and tinidazole;
20. Omeprazole and amoxicilline;
21. Omeprazole and azithromycine;
22. Omeprazole, bismuth and ciprofloxacine;
23. Omeprazole, bismuth and clarithromycine;
24. Omeprazole, clarithromycine and tinidazole;
25. Omeprazole and dirithromycine;
26. Omeprazole, lansoprazole and rebamipide;
27. Omeprazole, metronidazole and amoxicilline;
28. Omeprazole, metronidazole and azithromycine;
29. Omeprazole, metronidazole and clarithromycine;
30. Omeprazole and norfloxacine;
31. Omeprazole, sucralfate, metronidazole and tetracycline;
32. Omeprazole, clarithromycine and tinidazole;
33. Pantoprazole, clarithromycine and amoxicilline;
34. Pantoprazole and clarithromycine;
35. Ranitidine bismuth citrate, clarithromycine and tetracycline;
36. Ranitidine bismuth citrate and clarithromycine;
37. Ranitidine bismuth citrate, metronidazole and clarithromycine;
38. Ranitidine bismuth citrate and cefuroxime;
39. Rifaximin and erythromycine;
40. Omeprazole, bismuth, tretracycline and metronidazole;
41. Omeprazole, bismuth subcitrate, tretracycline and metronidazole;
42. Bismuth subcitrate, tretracycline and metronidazole.

SUMMARY OF THE INVENTION

An object of the present invention is to supply a new pharmaceutical dosage form for the administration of active principles in multiple therapies, comprising two capsules, one placed inside the other, and containing respectively one or more active principles.

An other object of the invention is the use of said pharmaceutical dosage form comprising two capsules one placed inside the other and containing respectively one or more active principles, in the therapy against the microorganisms Helicobacter pylori.

The pharmaceutical dosage form according to the invention is preferably used in triple or quadruple therapies against the microorganisms Helicobacter Pylori.

An advantage of the pharmaceutical dosage form of the invention is to be used in multiple therapies, which allows a simple and safe posology.

One of the major advantages of the pharmaceutical dosage form of the present invention is that it overcomes problems related with the interaction of the active principles by means of a physical barrier.

The purposes of this invention are reached, as indicated in claim 1, thanks to a pharmaceutical form which has the characteristics specified in the related claims.

The characteristics and advantages of the invention will be better understood after reading the following non restrictive description.

DETAILED DESCRIPTION OF THE INVENTION

Double Capsule

The present invention provides a pharmaceutical dosage form for the administration of active principles in multiple therapies featured by the presence of two capsules one placed inside the other and including respectively one or more active principles. This pharmaceutical dosage form is called double capsule and the two capsules are respectively called internal capsule and external capsule.

Both internal and external capsules are preferably made of hard gelatin. If desired, the internal capsule may be made of gelatin treated so as to make it gastroresistant or slow release.

The capsules already on the market are identified by numbers or letters according to their size (length, diameter and thickness), as indicated in Table 1 (CAPSUGEL MULTISTATE FILE, 2° Ed.)

TABLE 1: SIZE OF THE JELLY CAPSULES

Type of capsule	Format of Capsule	Total length of the capsule (nm +/- 0,3 nm)	Diameter of the external body (nm)	Thickness of the wall (nm)
CONI-SNAP SNAP-FIT	000	26,14	9,55	-
	00	23,3	8,18	0,231
	0+	23,8	7,36	0,224
	0	21,2	7,33	0,212
	1	19,0	6,63	0,216
	2	17,5	6,07	0,211
	3	15,6	5,57	0,203
	4	13,9	5,05	0,198
	5	11,0	4,64	0,173
CONI-SNAP SUPRO	A	18,00	8,18	0,231
	B	14,20	8,18	0,231
	C	13,50	7,33	0,224
	D	12,60	6,63	0,216
	E	11,60	6,07	0,211
LICAPS	0	21,70	7,33	0,224
	1	19,70	6,63	0,216
	2	17,90	6,07	0,211

Accordingly to the invention, the double capsule has an internal capsule smaller than the external one, since according to this principle all the combinations of the Table 1 are possible except for the combination of external capsule of format 0+ with internal capsule of format A or 0 of any types of capsules. Such combinations are chosen to facilitate the use for the patient and according to the quantity of substance to be introduced into the two capsules. As a matter of fact, the volume between the two capsules and the volume of the internal capsule should be suitable to allow the insertion of the quantities foreseen by the therapeutic dosage. The internal capsule should preferably be a 2 or 3 format, while the external capsule should be respectively a 0+ or 1 format.

In accordance with a preferred embodiment of the invention, an internal capsule of format 3 is inserted in an external capsule of format 0+.

Said pharmaceutical form is realised by means of an intermittent or continuous motion capsule filling machine equipped with dosators to feed empty capsules with powders, tablets, pellets or filled capsules. Exemples of said capsule filling machines are the Zanazi 40 of the company IMA in Bologna and the model MG Futura level 02 of the company MG2 in Bologna. As an alternative, the new double capsule can be realised by means of a manual machine type Zuma 150 or 300 and type Parke-Davis/Capsugel.

Besides, it must be taken into consideration that even the movement of the capsules caused by the capsule filling machines, either automatic or manual, and the simple act of inserting the internal capsule are enough to form between the two capsules a layer of powder which keeps them separated.

Triple Therapy

This pharmaceutical dosage form is particularly suitable to be used in a triple therapy for the eradication of the pathologic agents Helicobacter pylori (also known as Campilobacter pylori), consisting of the administration of three active principles which are a soluble salt of bismuth, a first antibiotic and a second antibiotic. Each internal and external capsule contains one or more active principles.

The bismuth salt is preferably selected from the group consisting of bismuth subcitrate, bismuth aluminate, bismuth carbonate, bismuth citrate, colloidal bismuth subnitrate, bismuth germanate, bismuth germanium oxide, bismuth nitrate, bismuth oxide, bismuth oxychloride, bismuth phosphate, bismuth salicylate, bismuth subcarbonate, bismuth subnitrate, bismuth subsalicylate, bismuth tribromophenate, bismuth trioxyde, bismuth vanadate, and bismuth vanadium tetraoxide. Bismuth salts may be used in a complex form. For example, bismuth biscalcitrate is a complex form of bismuth subcitrate.

The first antibiotic is selected from the group consisting of the nitroimidazoles. The nitroimidazoles are preferably selected from the group

consisting of metronidazole, apronidazole, azomycine, benzonidazole, carnidazole, demetridazole, etanidazole, flunidazole, misonidazole, nimorazole, ornidazole, panidazole, ronidazole, and tinidazole. Preferably, the first antibiotic is metronidazole.

The second antibiotic is selected from the group consisting of the macrolides and the compounds of the family of tetracyclines. The macrolides are preferably selected from the group consisting of azithromycine, clarithromycine and erythromycine. The compounds of the family of tetracyclines are preferably selected from group consisting of tetracycline, chlortetracycline, doxycycline, glycocycline, guamecycline, lymecycline, methacycline and sancycline. As known in the field, tetracycline correspond to tetracycline hydrochloride.

In accordance with a preferred embodiment of the invention, the external capsule contains bismuth subcitrate and metronidazole, and the internal capsule contains tetracycline.

When the external capsule, preferably containing bismuth subcitrate in a complex form and metronidazole, dissolves, it allows the complex bismuth to form a curative gel at the gastric level. After a certain period of time, according to the therapeutic indications, the internal capsule dissolves and releases tetracycline, which also acts at the gastric level.

The triple therapy as described above, usually consists of the administration of two identical double capsules several times a day, with no particular care as to the sequence of consumption and of the manipulation of the said double capsules. Ingestion of capsules is preferably done before meals and before a snack at bedtime.

Quadruple Therapy

An further way of realisation of the invention consists of the administration of a fourth active principle such as a K^+/Na^+ATP-ase inhibitor or a anti-H_2, together with the double capsule described above. In this case, the double capsule as foreseen by the invention will be destined to use in a quadruple therapy for the affections of the digestive system. K^+/Na^+ATP-ase inhibitor or

anti-H_2 is selected from group consisting of BY841; cimetidine; ebrotidine; etintidine; famotidine; flunarizine; ICI-162,846; lansoprazole; metiamide; mifentidine; niperotidine; nizatidine; omeprazole; oxmetidine; pantoprazole; rabeprazole; ramixotidine; ranitidine; ritanserin; roxatidine acetate hydrochloride; ZKF-93479; SKF-94482; sufotidine; tiotidine; TY-11345; Wy-45,727; and zaltidine. Preferably, omeprazole is used as K^+/Na^+ATP-ase inhibitor.

The K^+/Na^+ATP-ase inhibitor or anti-H_2 may be introduced in the external capsule, in the internal capsule or in a separate pharmaceutical form. Since it is a requirement that K^+/Na^+ATP-ase inhibitor or anti-H_2 reach the small intestine, it may be delivered embedded in the gastroresistant coated pellets, multiple small tablets or single tablet. Considering that K^+/Na^+ATP-ase inhibitor or anti-H_2 must be administered according to criteria other than those foreseen for triple therapy, double capsules without K^+/Na^+ATP-ase inhibitor or anti-H_2 may be alternatively administered to double capsules containing K^+/Na^+ATP-ase inhibitors or anti-H_2, following a therapeutic scheme prescribed by the physician, depending on the seriousness of the disease and the condition of the patient.

In accordance with another preferred embodiment of the invention, the external capsule contains bismuth subcitrate and metronidazole, and the internal capsule contains tetracycline and omeprazole.

Characteristics of the Invention

Preferably, both capsules contain excipients. These excipients are selected from the group consisting of magnesium stearate; talc; cellulose and its derivatives; silica and its derivatives; sugars; polyethylene-glycols; wax; mono-, di- and tri-glycerides of hydrogenated fat acids; alcohols and acids at high molecular weight; and relevant mixtures thereof.

Both internal and external capsule containing the active principles as described above are stable at a temperature comprised between 5 and 50°C and at a humidity comprised between 35 and 65%.

Scope of the Invention

Preferred embodiments of the invention have been described above for triple therapy and quadruple therapy for the eradication of Helicobacter pylori. Although these embodiments are preferred for such therapies, it should be understood that the double capsule may contain other active principles in accordance with the invention. Thus, the combinations of active principles listed above in the background of the invention, may be used in the claimed pharmaceutical dosage form without departing from the scope of the claimed invention. For example, using the above listed combination no. 34, a double capsule having an external capsule containing clarithromycine and an internal gastroresistant capsule containing pantoprazole would fall within the scope of the claimed invention.

The following are stabilisation and dissolution trials together with an example for the realisation of the double capsule as foreseen by the invention, for explanatory and not limitative purposes.

Stability Trials

Two products have been analysed, respectively a single capsule containing coated tetracycline hydrochloride, bismuth biscalcitrate, metronidazole and a double capsule as foreseen by the invention containing, in the internal capsule, non-coated tetracycline and, in the external capsule, bismuth biscalcitrate and metronidazole.

A sample for each product to be analysed has been incubated at room temperature, 37°C and 44°C for a period of 1 month. At the time zero and at the end of the incubation period (1 month), an analysis of the macroscopic characteristics of the products under analysis has been performed.

TIME ZERO

Single capsule

External capsule: white
Content: mixture of white powder (bismuth biscalcitrate) and yellow powder (tetracycline hydrochloride)

Double capsule

External capsule: white
Internal capsule: brown
Content of the External capsule: white powder (bismuth biscalcitrate, metronidazole)

Content of the internal capsule: yellow powder (tetracycline hydrochloride)

TABLE 2

AFTER 1 MONTH			
SINGLE CAPSULE	**ROOM TEMPERATURE**	**37°C**	**44°C**
External capsule	Slightly yellowish	White	white
Content	Mixture of white and yellow powder	Mixture of white and beige powder	Mixture of white and beige powder
DOUBLE CAPSULE	**ROOM TEMPERATURE**	**37°C**	**44°C**
External capsule	white	white	white
Internal capsule	brown	Brown	brown
Content of the External capsule	white powder	white powder	white powder
Content of the Internal capsule	yellow powder	yellow powder	yellow powder

As it can be observed in Table 2, at the temperatures 37°C and 44°C, the content of the single coated capsule forms a beige-coloured product while the double capsule as foreseen by the invention does not form any degradation

product. This effect is encouraged by the physical barrier represented by the coating of the internal capsule which does not allow the overflow of tetracycline.

Dissolution Trials

Five double capsules have been taken from one of the batches under examination, all five of them featured by the same characteristics:

External capsule of format	0+
containing	
bismuth biscalcitrate	215 mg
metronidazole	125 mg
Internal capsule of format	3
containing	
tetracycline hydrochloride	125 mg

The capsules have been analysed separately and under identical conditions according to the criteria of the Pharmacopoeia of the United States USP 23 Ed. for the dissolution trial.

The purpose of the trial is to check if the exact quantity of tetracycline hydrochloride contained in the internal capsules dissolves (as indicated in the above Pharmacopoeia, which complies with all the other Pharmacopoeias). In this case, the presence of the external capsule and of its components should not affect the quantity of material under dissolution nor the time taken to release the active principle tetracycline hydrochloride.

The quantity of material to be dissolved within 60 minutes must not be inferior to 80% of the quantity present in the capsule according to said limit, foreseen by the Pharmacopoeia.

As for the double capsules, the following percentage dissolution results have been obtained:

Minimum value of dissolution 81,4%

Maximum value of dissolution 107,9%

Average value 100,0%

RSD = 9,7% (RSD = Relative Standard Deviation)

From the results obtained, it is clear that the double capsule as described by the invention is in compliance with the foreseen dissolution characteristics.

Example 1

Capsules of format 3 have been prepared with the following content:

Tetracycline hydrochloride	125 mg
Gastroprotected omeprazole	5 mg
Magnesium stearate	5 mg
Talc	5 mg

Capsules of format 0+ have been prepared with the following content:

Bismuth biscalcitrate	215 mg (corresponding to 53,7 mg of Bismuth)
Metronidazole	125 mg
Magnesium stearate	5 mg
Talc	5 mg

The capsules 0+ have not been completely sealed, so that it will be possible to open them again with a manual machine (Zuma), and insert in the inside the capsule of format 3, previously prepared.

The capsules have then been sealed and subjected to the controls concerning the disaggregation time, the average weight of the content, the sealing procedure, the assay of the single components and the microbiological purity, as foreseen in the Pharmacopoeia.

Although preferred embodiments of the invention have been described in detail herein, it is to be understood that the invention is not limited to the precise embodiments and that various changes and modifications may be effected therein without departing from the scope or the spirit of the invention.

WHAT IS CLAIMED IS:

1. Pharmaceutical dosage form for the administration of active principles in multiple therapies comprising the presence of two capsules one placed inside the other and containing respectively one or more active principles.

2. Pharmaceutical dosage form as claimed in claim 1, wherein the internal capsule has a format between 2 or 3 and the external capsule has format between 0+ or 1.

3. Pharmaceutical dosage form as claimed in claim 2, wherein the external capsule has a format 0+ and the internal one has a format 3.

4. Pharmaceutical dosage form as claimed in any one of claims 1 to 3, wherein both internal and external capsules are made of hard gelatin.

5. Pharmaceutical dosage form as claimed in any one of claims 1 to 4, wherein the internal and external capsules contain respectively and independently one or more excipients.

6. Pharmaceutical dosage form as claimed in claim 5, wherein excipients is selected from the group consisting of magnesium stearate; talc; cellulose and its derivates; silica and its derivates; sugars; polyethyglycols; wax, mono-, di- and tri-glycerids of hydrogenated fat acids; alcohols and acids at high molecular weight; and relevant mixtures thereof.

7. Pharmaceutical dosage form as claimed in any one of claims 1 to 6, wherein the internal capsule is made of a gelatin giving it a gastroresistant or prolonged release effect.

8. Use of a pharmaceutical dosage form as claimed in any one of the claims 1 to 7, for the therapy against the microorganisms Helicobacter pylori.

9. Use of a pharmaceutical dosage form as claimed in any one of the claims 1 to 6, for a triple therapy against the microorganisms Helicobacter pylori wherein the external capsule comprises a soluble salt of bismuth and a first antibiotic, and the internal capsule comprises a second antibiotic.

10. Use of a pharmaceutical dosage form as claimed in any one of the claims 1 to 6, for a quadruple therapy against the microorganisms Helicobacter pylori wherein the external capsule comprises a soluble salt of bismuth and a first antibiotic, and the internal capsule comprises a second antibiotic, and a K^+/Na^+ATP-ase inhibitor or anti-H_2.

11. Use of a pharmaceutical dosage form as claimed in any one of the claims 1 to 6, for a quadruple therapy against the microorganisms Helicobacter pylori wherein the external capsule comprises a soluble salt of bismuth, a first antibiotic, and a K^+/Na^+ATP-ase inhibitor or anti-H_2; and the internal capsule comprises a second antibiotic.

12. Use of a pharmaceutical dosage form as claimed in any one of claim 1 to 6, for a quadruple therapy against the microorganisms Helicobacter pylori wherein in addition to this pharmaceutical form, use is simultaneously made of another pharmaceutical dosage form comprising a K^+/Na^+ATP-ase inhibitor or anti-H_2.

13. Use as claimed in any one of claims 9 to 12, wherein the bismuth salt is selected from the group consisting of bismuth subcitrate, bismuth aluminate, bismuth carbonate, bismuth citrate, colloidal bismuth subnitrate, bismuth germanate, bismuth germanium oxide, bismuth nitrate, bismuth

oxide, bismuth oxychloride, bismuth phosphate, bismuth salicylate, bismuth subcarbonate, bismuth subnitrate, bismuth subsalicylate, bismuth tribromophenate, bismuth trioxyde, bismuth vanadate, and bismuth vanadium tetraoxide.

14. Use as claimed in claim 13, wherein the bismuth salt is bismuth subcitrate.

15. Use as claimed in any one of claims 9 to 14, wherein the first antibiotic is selected from the group consisting of the nitroimidazoles.

16. Use as claimed in claim 15, wherein the nitroimidazoles are selected from the group consisting of metronidazole, apronidazole, azomycine, benzonidazole, carnidazole, demetridazole, etanidazole, flunidazole, misonidazole, nimorazole, ornidazole, panidazole, ronidazole, and tinidazole.

17. Use as claimed in claim 16, wherein the nitroimidazole is metronidazole.

18. Use as claimed in one of claims 9 to 17, wherein the second antibiotic is selected from the group consisting of the macrolides and the compounds of the family of tetracyclines.

19. Use as claimed in claim 18, wherein the macrolides are selected from the group consisting of azithromycine, clarithromycine and erythromycine.

20. Use as claimed in claim 18, wherein the compounds of the family of tetracyclines are selected from group consisting of tetracycline, chlortetracycline, doxycycline, glycocycline, guamecycline, lymecycline, methacycline and sancycline.

21. Use as claimed in claim 18 or 20, wherein wherein the second antibiotic is tetracycline.

22. Use as claimed in any one of claims 10 to 12, wherein the K^+/Na^+ATP-ase inhibitor or anti-H_2 is selected from group consisting of BY841; cimetidine; ebrotidine; etintidine; famotidine; flunarizine; ICI-162,846; lansoprazole; metiamide; mifentidine; niperotidine; nizatidine; omeprazole; oxmetidine; pantoprazole; rabeprazole; ramixotidine; ranitidine; ritanserin; roxatidine acetate hydrochloride; ZKF-93479; SKF-94482; sufotidine; tiotidine; TY-11345; Wy-45,727; and zaltidine.

23. Use as claimed in claim 22, wherein omeprazole is selected.

24. Use as claimed in any one of claims 9 to 23, wherein both internal and external capsules are stable at a temperature comprised between 5 and 50°C and at a humidity comprised between 35 and 65%.